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(57) Abstract

The invention relates to a method of cleaning, disinfecting and preserving contact lenses comprising treating contact lenses in the following order with: 1) at least one enzyme, 2) at least one enzyme inhibitor, 3) at least one disinfecting agent, and 4) optionally rinsing in e.g. physiological saline solution. A contact lens product, a tablet or capsule for cleaning, disinfecting and preserving contact lenses, and the use of an enzyme inhibitor are also disclosed.

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Title: Cleaning, disinfecting and preserving contact lenses

FIELD OF THE INVENTION

The present invention relates to a method of cleaning, disinfecting and preserving contact lenses, a contact lens cleaning, disinfecting and preserving product, a tablet or capsule for cleaning, disinfecting and preserving contact lenses and the use of an enzyme inhibitor for cleaning, disinfecting and preserving contact lenses.

BACKGROUND OF THE INVENTION

To enjoy the advantages gained by wearing contact lenses it is necessary to carry out the time consuming and cumbersome task of cleaning and disinfection the contact lenses. The procedure differs depending on the type of contact lenses in question e.g. hard lenses or soft lenses.

In all cases, the contact lenses need to be cleaned and disinfected periodically, to avoid infection and discomfort for the wearer, in some cases every morning or evening.

When removed from the eyes the lenses must be stored in a preserving solution. Before wearing the lenses again they must be cleaned, disinfected and rinsed.

The cleaning operation is carried out to remove deposits and debris from the surface of the contact lenses. The cleaning effect is often obtained by treatment with enzymes such as proteases, capable of hydrolysing proteinaceous material to smaller water-soluble subunits.

Disinfection of the contact lenses prevents growth of bacteria on the contact lenses which might lead to infection of the eyes

and making it impossible to wear contact lenses for a long period of time. Disinfecting agents such as hydrogen peroxide is widely used.

After the cleaning and/or disinfecting procedure the contact lenses need to be rinsed, to make sure that all enzymatic activities and/or disinfecting agent are removed, e.g. by using a physiological saline solution.

When the contact lenses are not worn the lenses need to be stored under sanitary conditions to secure that they are ready in a clean state for the next wear.

Further it is also important to make sure that the lenses are treated with care to secure that e.g. the shape of the contact lenses is maintained, staining of the lenses is prevented, an acceptable oxygen permeability of the lenses is maintained etc.

Soil deposits are found on all groups of contact lenses, but the easiness of removal differs among the groups. Hard contact lenses are easy to clean, due to only small amounts of soil deposited, and ease of removing soil by rubbing. Soft hydrophillic lenses are more prone to adsorption of soil which is difficult to remove. One reason is that hard rubbing and abrasives might damage the lens.

The major important soil deposits on contact lenses are proteins, lipid deposits and Jelly bumps, mucins, pigments and inorganic compounds.

Wedler (J. Biomed. Mater. Res. Vol. 11, p. 525-535, 1977) has identified tear proteins from extracts of contact lenses. Per lens was found 5-10 μg protein, 1.0-1.2 μg carbohydrates, 5-25 μg phospholipids. Cholesterol and glucose were not detected. Albumin, lysozyme, IgG and α_1-lipoprotein were found in the deposits.

The main component of Jelly bumps deposits are lipids (Bilbaut et al., Exp. Eys. Res., Vol. 43, p. 153-165, 1986). These are often seen on contact lenses with high water content, particularly extended wear contact lenses (Pohlzhofer, Deutsche Optiker Zeitung, Vol. 40, p.40-100, 1985 and Sack et al. Investigative Ophthalmology & Visual Science, Vol. 28, p. 842-849, 1987).

A plethora of methods for removing deposits from contact lenses are known. Contact lenses are often cleaned with enzymes. US patent nr. 3,910,296 (Allergan) describes a method for cleaning contact lenses by the use of a protease.

US patent nr. 4,670,178 (Allergan) discloses a method for simultaneous cleaning and disinfection contact lenses with a protease in hydrogen peroxide. The cleaning is effected by protease and shown to be very efficient.

CA 1,146,881 (Bedding) points out a method for cleaning contact lenses using enzymes, where the cleaning procedure is followed by rinsing of the lenses, e.g. with saline, to remove active enzymes from the lens.

EP patent nr. 257.942 (Hoya Corporation) describes a contact lens cleaning kit comprising an oxidising agent and reducing agent in such a form that they do not react with each other in the kit. When placed in the water, at the same time, the major portion of the oxidant dissolves more rapidly than the major portion of the reductant. The lenses can be worn immediately after treatment without the need for water washing.

CA patent application nr. 2,044,072 (Webb), WO 93/17720 (Webb) and EP patent application nr. 196,151 (Hopkinson) disclose chloramine-T used for disinfecting contact lenses. No use of proteases is mentioned in these patent documents.

US patent nr. 5,057,414 (Stief et al.) concerns determining activity of serine proteases and inhibitors in plasma, includ-

ing treatment with e.g. chloramine-T or chloramine-B as an oxidizing agent and a detergent to inactivate specific inhibitors. The patent does not concern cleaning or disinfecting of contact lenses.

EP patent application nr. 147,100 (Ciba Geigy) concerns cleaning and disinfecting of contact lenses with a hydrogen peroxide solution in the presences of a solid sustained release composition which slowly releases a peroxide inactivator. The lenses may be treated with a wetting or comfort solution before inserting into the eyes. However, cleaning and disinfection with hydrogen peroxide does not remove proteinaceous deposits effectively from the surface of the contact lenses.

EP patent application nr. 279.401 (Dr. Thilo & Co. Gmbh) discloses a disinfection and cleaning product for contact lenses containing a chlorine releasing compound, at least one protease and conventional formulation assistants. Initially the chlorine releasing compound, which must be characterized as a strong disinfecting agent, is added to the solution. After sufficient disinfecting, the protease is added to clean the lenses by degrading protein deposits on the lenses surface. The remaining chlorine releasing compound is inactivated by the protease. After the disinfecting and cleaning process the contact lenses must be rinsed thoroughly to remove active protease to avoid damage of the eyes.

A drawback of the techniques disclosed in the prior art documents is that the cleaning and disinfecting of contact lenses with enzymes must be succeeded by a thorough rinsing procedure to secure removal of all remaining enzyme activity before inserting the contact lenses into the eyes. This makes the procedures cumbersome and implies a risk of forgetting the rinsing step, which may lead to exposing the eyes to enzymatic activity and/or disinfecting agents, which will irritate or even might damage the eyes.

SUMMERY OF THE INVENTION

It is the object of the invention to provide a facilitated and secure method for simultaneous cleaning, disinfecting and preserving contact lenses, which allows the contact lens wearer to insert the contact lenses after cleaning and disinfection, without additional rinsing or washing or followed by only sparingly rinsing.

The above mentioned problems are overcome by a method for simultaneous cleaning, disinfecting and preserving contact lenses comprising treating contact lenses in the following order with:

1) at least one enzyme,
2) at least one enzyme inhibitor,
3) at least one mild disinfecting agent, and
4) optionally rinsing in e.g. a physiological saline solution.

According to a preferred embodiment of the invention the enzyme inhibitor is a carbonyl hydrolase inhibitor, which is also a mild disinfecting agent.

In a specific embodiment of the invention the enzyme inhibitor is chloramine-T or chloramine-B.

A second object of the invention is to provide a contact lens cleaning, disinfecting and preserving product, comprising at least one enzyme, at least one enzyme inhibitor and at least one mild disinfecting agent.

Another object of the invention is to provide a tablet or capsule for cleaning, disinfecting and preserving contact lenses comprising at least one enzyme inhibitor.

In an embodiment of the tablet or capsule of the invention said enzyme inhibitor is released slowly or delayed to the aqueous solution.

Still another object of the invention is to provide for the use of an enzyme inhibitor for cleaning, disinfecting and preserving contact lenses.

In a specific embodiment of the invention chloramine-T or chloramine-B is used as said enzyme inhibitor.

DETAILED DESCRIPTION OF THE INVENTION

The present invention can be used with all groups of contact lenses including hard, soft, rigid gas permeable lenses and silicone lenses. Nevertheless, the invention is preferably employed with cleaning and disinfecting soft hydrogel lenses which absorb significant amounts of water.

Hydrogel lenses are commonly prepared from monomers or polymers, such as N,N-dimethyl acylamide, 2-hydroxyethyl methacrylate, hydroxyethylmethyl methacrylate, N-vinyl pyrrolidone, poly vinyl pyrrolidone, vinyl acetate, glyceryl methacrylate, flour silicon methacrylate, butyl methacrylate, isobutyl methacrylate, 3-methoxy-2-hydroxypropyl methacrylate, pentyl methacrylate, cyclohexyl methacrylate, alkyl methacrylate, glycerol methacrylate, methyl methacrylic acid, methacrylic acid or methacrylic acid ester, and the like.

The object of the invention is to provide a facilitated and secure method for simultaneously cleaning, disinfecting and preserving contact lenses comprising treating contact lenses in the following order with:

1) at least one enzyme,
2) at least one enzyme inhibitor,
3) at least one disinfecting agent, and
4) optionally rinsing in e.g. physiological saline solution.

According to the present invention the enzyme used as a cleaning agent is added before the mild disinfection agent

and/or the enzyme inhibitor. This will secure that the eyes will not be damaged even if the rinsing procedure is not used or forgotten.

The optional rinsing step is performed to make sure that the remaining disinfecting agent is removed from the lenses. It is to be understood that the step may be superflous and may be left out, due to the use of a mild disinfecting agent which is acceptable for the eyes.

In this case it is possible to use only one solution to clean, disinfect and store contact lenses, which makes the method less cumbersome in comparison to prior art methods.

If the enzyme inhibitory effect is reversible the optional rinsing step is mandatory. This is due to the risk that the inhibitory effect of the enzyme inhibitor ceases to exist, e.g. when diluted in an aqueous solution or tear solution, change of the physical conditions, such as pH and ionic strength, the presence of other components etc.

However, it is to be understood that this does not imply that it is mandatory that the enzyme inhibitor is an irreversible enzyme inhibitor, but it is required that the enzyme inhibitor inhibit enzyme activity to such an extend that the eyes are not damaged during wear of the contact lenses.

In an embodiment of the invention said contact lenses are first immersed in an aqueous solution, secondly treated with at least enzyme, for a period of time sufficient to degrade deposits on the contact lenses' surface, then treated with at least one enzyme inhibitor for a period of time sufficient to inhibit remaining enzyme, and finally disinfected.

The enzymes used for the cleaning of contact lenses according to the invention are carbonyl hydrolases, which exhibits proteolytic, lipolytic, amylolytic or related activities.

The enzymes may be neutral, acidic or alkaline. However, it is preferred that the enzymes have substantial activity at pH between 6.0 and 8.5.

Preferred enzymes used for the cleaning process are proteases selected from the group comprising serine proteases, acidic aspartic proteases, cysteine proteases and metallo proteases, respectively. As suitable enzymes are also contemplated truncated, modified enzymes or variants of the above listed groups.

Examples of preferred serine proteases are e.g. trypsins, chymotrypsins and subtilisins.

Most preferred are the Bacillus derived alkaline serine proteases, such as subtilisin BPN', subtilisin Carlsberg, subtilisin PB92, subtilisin 309, subtilisin 147, subtilisin 168, subtilisin DY, aqualysin or thermitase, truncations, modification and variants thereof.

Specific examples of cysteine proteases are e.g. papain and bromelain.

To the group of suitable metallo proteases are e.g. Neutrase® and collagenase.

Specific examples of acidic aspartic proteases are e.g. pepsin A, pepsin B, pepsin C, chymosin, cathepsin B and renin.

In an embodiment of the invention the enzyme inhibitor is a carbonyl hydrolase inhibitor. Also contemplated are reversible enzyme inhibitors acting as irreversible enzyme inhibitors under the conditions present in the eyes.

Examples of metallo protease inhibitors are EDTA and metal chelating agents.

Specific examples of enzymes that inhibit serine proteases are chloramine-T and chloramine-B.

In a preferred embodiment of the invention said enzyme inhibitor exhibits a mild disinfecting effect on the contact lenses.

Chloramine-T and chloramine-B are specific examples of compounds exhibiting enzyme inhibitory effect as well as disinfecting effect.

Other examples of combined enzyme inhibitors/disinfectants are bacitracin and aryl boronic acids.

According to the invention the enzyme is present in a concentration sufficient for degrading deposits on the surface of the contact lenses and the enzyme inhibitor is present in a concentration sufficient to inhibit all remaining enzyme activity.

The specific amounts of enzyme and enzyme inhibitor are easily determined by one skilled in the art and are dependent upon the time allowed for removing the deposits, the activity of the enzyme and enzyme inhibitor, the purity of the enzyme etc.

In a specific embodiment of the invention chloramine-T is used as the enzyme inhibitor and the disinfecting agent. Chloramine-T is present in a concentration of 0.0001% to 5%, preferably of 0.001% to 1%.

Another object of the invention is to provide a contact lens cleaning, disinfecting and preserving product, comprising at least an enzyme and at least an enzyme inhibitor.

In an embodiment of the invention the product comprises an aqueous solution and a tablet. Said solution preferably comprises an enzyme and said tablet comprises an enzyme inhibitor.

In another embodiment of the invention the contact lens product comprises at least two tablets, one of which comprises said enzyme and the other comprises said enzyme inhibitor.

Preferably the product comprises a multi layer tablet, wherein an outer layer or coating comprises said enzyme(s) and an inner layer or core comprises said disinfecting agent and enzyme inhibitor. Said core and outer layer may be separated by a barrier or a membrane.

Said barrier may in an embodiment of the invention be made of a water soluble polymer layer, preferably a water soluble film.

Examples of said water soluble film comprises polymers soluble in an acidic medium, such as polymers of dimethylaminomethacrylate and neutral methacrylate esters.

Alternatively the film comprises a pH neutral soluble polymer. Suitable polymers are e.g. soluble cellulose ethers, such as methylcellulose, methylhydroxycellulose, methylhydroxyethylcellulose, hydroxypropylcellulose, hydroxyethylcellulose, sodium carboxymethylcellulose, cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, a polymer of methacrylic acid and methacrylate esters, a copolymer of methacrylic acid and methacrylate esters, a copolymer of methyl vinyl ether and maleic acid anhydride and polyvinyl alcohols.

In still another embodiment the contact lens product comprises a tablet comprising a sparingly soluble matrix comprising the enzyme(s) wherein the enzyme inhibitor is dispersed or distributed.

In a preferred embodiment the tablet is a controlled release tablet.

Suitable plasticizers of polyhydric alcohols and water may be added to the above listed soluble film polymers to control the diffusion rate. Preferred plasticizers for this purpose are 1,2-propylene glycol, polyethylene glycols and citrate esters.

In a specific example the enzyme inhibitor is chloramine-T or chloramine-B, preferably present in a concentration of 0.0001% to 5%, preferably 0.001% to 1%.

Considered as suitable enzyme inhibitors are also peptide aldehydes, peptide ketones, such as peptide chloromethyl ketones, and cyclic peptides, such as bacitracin, and aryl boronic acids.

Suitable enzymes which may be used according to the invention are mentioned above.

Still another object of the invention is to provide a tablet or capsule for cleaning, disinfecting and preserving contact lenses, comprising an enzyme inhibitor, which may further comprise an enzyme.

In a specific embodiment of the invention the tablet or capsule comprises chloramine-T or chloramine-B as the enzyme inhibitor.

In a preferred embodiment the tablet or capsule is of the controlled release type, wherein said enzyme is first released and said enzyme inhibitor is released after a time sufficient for the said enzyme to degrade composites on the contact lenses.

In an alternative embodiment said enzyme inhibitor is released slowly or delayed to the aqueous solution.

A final object of the invention is to provide for the use of an enzyme inhibitor in the cleaning, disinfecting and preserving of contact lenses. The enzyme inhibitor may be selected from the group of compounds mentioned above, such as a carbonyl hydrolases.

In a specific embodiment the enzyme inhibitor is chloramine-T or chloramine-B.

According to the invention the disinfecting agent used must be a mild disinfecting agent.

Additional components may be added to or incorporated into the tablets or capsules which do not substantially decrease the activity of the active components.

Examples are components such as effervescing agents, stabilizers, buffers, chelating agent and/or sequestering agents, colouring agent, tonicity adjusting agents, surfactant and the like. In addition binders, lubricants, carriers, and other excipients normally used in producing tablets may be incorporated.

Examples of suitable buffering agent include alkali metal salts, such as potassium or sodium carbonates, acetates, borates phosphates, citrates, and hydroxides, and weak acids such as acetic and boric acids.

Effervescing agents are typically employed when the enzyme is provided i solid form. Examples of suitable effervescing agent include, tartaric or citric acid used in combination with suitable alkali metal salts, such as sodium carbonate.

In the case of the cleaning, disinfecting and preserving product comprising an aqueous solution, it may contain one or more of suitable buffering agents (as listed above), chelating agents and/or sequestering agent, tonicity adjusting agent and surfactant.

Suitable tonicity adjusting agents include sodium and potassium chloride, dextrose, calcium and magnesium chloride.

Suitable surfactants can either be cationic, anionic, nonionic or amphoteric. Preferred surfactants are neutral or nonionic.

Specific examples include polyethylene glycol ethers of fatty acids, polyoxypropylene ethers of C12-C18 alkanes and polyxye-

thylene, polyoxypropylene block copolymers of ethylene diamine (i.e. poloxamine).

Examples of preferred chelating agents include Ethylenediaminetetraacetic acid (EDTA) and its salts (disodium) and certain polyvinyl alcohols.

MATERIALS AND METHODS

Enzymes:

Savinase® : Alcalophilic subtilisin from Bacillus lentus
Subtilisin A®: Subtilisin Carlsberg type
Esperase® : Alcalophilic subtilisin from Bacillus lentus

All enzymes are available from Novo Nordisk A/S.

Chloramine-T:

Chloramine T (Trihydrate) p.a. Merck art 2426
Mw = 281.69 g/mol, 1% equals approx. 36 mM

Protease activity analysis with Suc-Ala-Ala-Pro-Phe-pNA:

The substrate (succinyl-Alanine-Alanine-Proline-Phenylalanine-para-nitroanilide. Sigma no. S-7388,
Mw 624.6 g/mole.

Proteases especially chymotrypsin cleaves the bond between the peptide and p-nitroaniline to give a visible yellow colour absorbing at 405 nm.

Buffer: e.g. Britton and Robinson buffer pH 8.3
Substrate: 100 mg suc-AAPF-pNA is dissolved into 1 ml dimethyl sulfoxide (DMSO). 100 µl of this is diluted into 10 ml with Britton and Robinson buffer.

Analysis: Substrate and protease solution is mixed and the absorbance is monitored at 405 nm as a function of time and $ABS_{405\ nm}$/min. The temperature should be controlled (20-50°C

depending on protease). This is a measure of the protease activity in the sample.

Contact lenses:
Revolution, Sunsoft, type 4

Buffer:
0.05 M K-phosphate
Britton and Robinson buffer pH 8.3

Solutions:
Solution A: 1 mg/ml solution of suc-Alanine-Alanine-Proline-Phenylalanine-para-nitroanilide (s-AAPF-pNA)
Substrate: 100 mg suc-AAPF-pNA is dissolved into 1 ml dimethyl sulfoxide (DMSO). 100 µl of this is diluted into 10 ml with Britton and Robinson buffer.

Procedures:
Test for the inhibitory effect of chloramine-T
The enzyme is incubated for 5 minutes, 1 hour, 4 hours and 27 hours in MilliQ-water and 0.9% NaCl aqueous solution as incubation solutions with and without chloramine-T. Then protease activity analysis are performed, using the suc-AAPF-pNA method, and using a non-incubated enzyme solution as a blind.

The incubation solutions are diluted to $3*10^{-4}$ and $3*10^{-5}$ KNPU(S)/ml.

Test for protease activity on contact lenses
A contact lens (sunsoft) is soaked in 1.5 ml of the protease solution for 20 hours at room temperature.

The lens is rinsed in buffer and divided into two.
One half lens is then soaked for 1 hour in 1% chloramine-T in buffer, the other half lens is soaked in buffer.

Thereafter the residual protease activity on the lens is measured by applying 7.5 µl of solution A and incubated in a sealed container for 20 minutes.

Protease activity will cause solution A to hydrolyse and produce a yellow colour on the surface of the lenses.

EXAMPLES

Experiments

The following experiments were preformed as described in the section "METHODS AND MATERIALS".

All enzymes and solutions used are described in the section "METHODS AND MATERIALS".

Example 1

Experiment A:

The inhibitory effect of chloramine-T was tested on Savinase® in MilliQ-water (table 1) and 0.9% NaCl aqueous solution (table 2):

In table 1 and table 2 the results of the analysis are displayed.

TABLE: 1

	1% Chloramine-T		0.1% Chloramine-T		0.01% Chloramine-T	
	$3*10^{-5}$ KNPU per ml	$3*10^{-4}$ KNPU per ml	$3*10^{-5}$ KNPU per ml	$3*10^{-4}$ KNPU per ml	$3*10^{-5}$ KNPU per ml	$3*10^{-4}$ KNPU per ml
5 min	0	0	0	0	0	6
1 h	0	0	0	0	0	2
4 h	0	0	0	0	0	0
27 h	0	0	0	0	0	0

The inhibitory effect of chloramine-T on Savinase® in MilliQ-water as % remained enzyme activity.

TABLE: 2

	1% Chloramine-T		0.1% Chloramine-T		0.01% Chloramine-T	
	$3*10^{-5}$ KNPU per ml	$3*10^{-4}$ KNPU per ml	$3*10^{-5}$ KNPU per ml	$3*10^{-4}$ KNPU per ml	$3*10^{-5}$ KNPU per ml	$3*10^{-4}$ KNPU per ml
5 min	0	0	2	3	5	6
1 h	3	0	3	0	6	5
4 h	2	0	0	0	3	2
27 h	0	0	0	0	0	0

The inhibitory effect of chloramine-T on Savinase® in 0.9% NaCl aqueous solution as % remained enzyme activity.

Experiment B:

The inhibitory effect of chloramine-T was tested on subtilisin A in MilliQ-water (table 3) and in a 0.9% NaCl aqueous solution (table 4):

In table 3 and table 4 the results of the analysis are displayed.

TABLE: 3

	1% Chloramine-T		0.1% Chloramine-T		0.01% Chloramine-T	
	$3*10^{-5}$ KNPU per ml	$3*10^{-4}$ KNPU per ml	$3*10^{-5}$ KNPU per ml	$3*10^{-4}$ KNPU per ml	$3*10^{-5}$ KNPU per ml	$3*10^{-4}$ KNPU per ml
5 min	0	0	0	0	4	6
1 h	0	0	2	0	3	0
4 h	0	0	0	0	0	0
27 h	0	0	0	0	0	0

The inhibitory effect of chloramine-T on subtilisin A in MilliQ-water as % remained enzyme activity.

TABLE 4:

	1% Chloramine-T		0.1% Chloramine-T		0.01% Chloramine-T	
	$3*10^{-5}$ KNPU per ml	$3*10^{-4}$ KNPU per ml	$3*10^{-5}$ KNPU per ml	$3*10^{-4}$ KNPU per ml	$3*10^{-5}$ KNPU per ml	$3*10^{-4}$ KNPU per ml
5 min	0	0	0	0	2	4
1 h	0	0	2	0	3	0
4 h	0	0	0	0	2	0
27 h	0	0	0	0	0	0

The inhibitory effect of chloramine-T on subtilisin A in 0.9% Nail aqueous solution as % remained enzyme activity.

Experiment C:

The inhibitory effect of chloramine-T was tested on Esperase® in MilliQ-water (table 5) and in a 0.9% Nail aqueous solution (table 6):

In table 5 and table 6 the results of the analysis are displayed.

TABLE 5

	1% Chloramine-T		0.1% Chloramine-T		0.01% Chloramine-T	
	$3*10^{-5}$ KNPU per ml	$3*10^{-4}$ KNPU per ml	$3*10^{-5}$ KNPU per ml	$3*10^{-4}$ KNPU per ml	$3*10^{-5}$ KNPU per ml	$3*10^{-4}$ KNPU per ml
5 min	0	0	0	0	8	9
1 h	0	0	0	0	5	3
4 h	0	0	0	0	0	2
27 h	0	0	0	0	0	0

The inhibitory effect of chloramine-T on Esperase® in MilliQ-water as % remained enzyme activity.

TABLE 6

	1% Chloramine-T		0.1% Chloramine-T		0.01% Chloramine-T	
	$3*10^{-5}$ KNPU per ml	$3*10^{-4}$ KNPU per ml	$3*10^{-5}$ KNPU per ml	$3*10^{-4}$ KNPU per ml	$3*10^{-5}$ KNPU per ml	$3*10^{-4}$ KNPU per ml
5 min	0	0	6	5	16	16
1 h	0	0	0	0	11	7
4 h	0	0	0	0	4	5
27 h	0	0	0	0	0	3

The inhibitory effect of chloramine-T on Esperase® in 0.9% Nail aqueous solution as % remained enzyme activity.

Example 2

Test of the protease activity on contact lenses

Solutions of 0,01 KNPU Savinase/ml, 0.01 M KNPU Esperase®/ml, and 0,002 subtilisin A AU/ml, respectively, all in K-phosphate buffer, were tested for protease activity, as described above under "Methods and Materials".

All lenses soaked in buffer showed the presence of active protease on the lens after rinsing.

All lenses soaked with chloramine-T showed no protease activity. This result indicated that even adsorbed protease can be inhibited by adding an enzyme inhibitor.

As will be apparent to those skilled in the art in the light of the foregoing disclosure, many alterations and modifications are possible in the practice of this invention without departing from the spirit or scope thereof. Accordingly, the scope of the invention is to be construed in accordance with the substance defined by the following claims.

PATENT CLAIMS

1. A method of cleaning, disinfecting and preserving contact lenses comprising treating contact lenses in the following order with:

1) at least one enzyme,
2) at least one enzyme inhibitor,
3) at least one disinfecting agent, and
4) optionally rinsing in e.g. physiological saline solution.

2. The method according to claim 1, wherein the said contact lens is:

1) immersed in an aqueous solution,
2) treated with an enzyme, for a period of time sufficient to degrade deposits on the contact lenses' surface,
3) treated with an enzyme inhibitor for a period of time sufficient to inhibit remaining enzyme, and
4) disinfected.

3. The method according to the claims 1 to 2, wherein the enzyme is a carbonyl hydrolase, preferably a protease, such as an acidic aspartic protease, a cysteine protease, serine protease or a metallo protease.

4. The method according to the claim 3, wherein the enzyme is an acidic aspartic protease, such as pepsin A, B or C, or cathepsin D.

5. The method according to the claim 3, wherein the enzyme is a cysteine protease, such as papain.

6. The method according to the claim 3, wherein the enzyme is a metallo protease, such as Neutrase®.

7. The method according to the claim 3, wherein the enzyme is a serine protease, preferably of the subtilisin type, including alkalophilic subtilisins.

8. The method according to the claims 1 to 7, wherein the enzyme inhibitor is a carbonyl hydrolase inhibitor.

9. The method according to any of the claims 1 to 8, wherein the enzyme is present in a concentration sufficient for degrading deposits on the surface of the contact lenses and the enzyme inhibitor is present in a concentration sufficient to inhibit all remaining enzyme.

10. The method according to any of the claims 1 to 9, wherein said disinfecting agent is also an enzyme inhibitor.

11. The method according to any of the claims 1 to 10, wherein the enzyme inhibitor is chloramine-T or chloramine-B.

12. The method according to any of the claims 1 to 10, wherein the enzyme inhibitor is selected from the group of peptide aldehydes, peptide ketones, such as peptide chloromethyl ketones, cyclic peptides, such as bacitracin and aryl boronic acids.

13. The method according to claim 11, wherein chloramine-T or chloramine-B is present in a concentration of 0.0001% to 5%, preferably 0.001% to 1%.

14. A contact lens cleaning, disinfecting and preserving product, comprising at least one enzyme and at least one enzyme inhibitor.

15. The contact lens product, according to claim 14, comprising an aqueous solution and a tablet.

16. The contact lens product, according to claim 15, wherein said solution comprises an enzyme and said tablet comprises an enzyme inhibitor.

17. The contact lens product, according to claim 14, comprising at least two tablets, one of which comprises said enzyme and the other comprises said enzyme inhibitor.

18. The contact lens product, according to claim 14, comprising a multi layer tablet, wherein an outer layer or coating comprises said enzyme(s) and an inner layer or core comprising said disinfecting agent and enzyme inhibitor.

19. The contact lens product, according to claim 18, wherein said core and outer layer are separated by a barrier or a membrane.

20. The contact lens product, according to claim 19, wherein said barrier is a water soluble polymer layer, preferably a water soluble film.

21. The contact lens product, according to claim 20, wherein said soluble polymer layer, comprises compounds selected from the group of polymers of dimethylaminomethacrylate, soluble cellulose ethers, such as methylcellulose, methylhydroxycellulose, methylhydroxyethylcellulose, hydroxypropylcellulose, hydroxyethylcellulose, sodium carboxymethyl cellulose, cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, a polymer of methacrylic acid and methacrylate esters, a copolymer of methacrylic acid and methacrylate esters, a copolymer of methyl vinyl ether and maleic acid anhydride, and polyvinyl alcohols.

22. The contact lens product, according to the claims 18 or 19, wherein said tablet also comprises a plasticizer, such as polyhydric alcohols, preferable 1,2-propylene glycol, polyethylene glycols and citrate esters.

23. The contact lens product, according to claim 14, comprising a tablet comprising a sparingly soluble matrix comprising the enzyme(s), wherein the enzyme inhibitor is dispersed or distributed.

24. The contact lens product, according to claim 14, comprising a controlled release tablet.

25. The contact lens product, according to any of the claims 14 to 24, wherein the enzyme inhibitor is chloramine-T or chloramine-B.

26. The contact lens product according to claim 25, wherein chloramine-T or chloramine-B is present in a concentration of 0.0001% to 5%, preferably 0.001% to 1%.

27. The contact lens product, according to any of the claims 14 to 24, wherein the enzyme inhibitor is selected from the group of peptide aldehydes, peptide ketones, such as peptide chloromethyl ketones, cyclic peptides, such as bacitracin, and aryl boronic acids.

28. The contact lens product, according to claim 14 to 24, wherein the enzyme is a carbonyl hydrolase, preferably a protease such as a serine protease, especially of the subtilisin type including alkalophilic subtilisins.

29. A tablet or capsule for cleaning, disinfecting and preserving contact lenses, comprising an enzyme inhibitor.

30. The tablet or capsule according to claim 29 further comprising an enzyme.

31. The tablet or capsule according to claim 29 to 30, wherein the enzyme is a carbonyl hydrolase, preferably a protease, such as an acidic aspartic protease, a cysteine protease, serine protease or a metallo protease.

32. The tablet or capsule according to claim 30 to 31, wherein the enzyme is an acidic aspartic protease, such as pepsin A, B or C, or cathepsin B.

33. The tablet or capsule according to claim 30 to 31, wherein the enzyme is a cysteine protease, such as papain.

34. The tablet or capsule according to claim 30 to 31, wherein the enzyme is a metallo protease, such as Neutrase®.

35. The tablet or capsule according to claim 30 to 31, wherein the enzyme is a serine protease, preferably of the subtilisin type, including alkalophilic subtilisins.

36. The tablet or capsule according to claim 35, wherein the said serine protease is a subtilisin, such as subtilisin BPN', subtilisin Carlsberg, subtilisin PB92, subtilisin 309, subtilisin 147, subtilisin 168, subtilisin DY, aqualysin or thermitase, truncations, modifications and variants thereof.

37. The tablet or capsule according to claim 29, wherein the enzyme inhibitor is chloramine-T or chloramine-B.

38. The tablet or capsule of any of the claims 29 to 37, which is of the controlled release type, wherein said enzyme is first released and said enzyme inhibitor is released after a time sufficient for said enzyme to degrade composites on the contact lenses.

39. The tablet or capsule of any of the claims 29 to 38, wherein said enzyme inhibitor is released slowly.

40. A tablet or capsule of any of the claims 29 to 39, wherein said enzyme inhibitor is released delayed.

41. Use of an enzyme inhibitor in the cleaning, disinfecting and preserving of contact lenses.

42. The use of an enzyme inhibitor according to claim 41, wherein the enzyme inhibitor is a carbonyl hydrolase inhibitor.

43. The use of a enzyme inhibitor according to claim 41 to 42, wherein the enzyme inhibitor is chloramine-T or chloramine-B.

44. The use of a enzyme inhibitor according to claim 41 to 43, wherein the enzyme inhibitor is selected from the group of peptide aldehydes, peptide ketones, such as peptide chloromethyl, cyclic peptides, such as bacitracin, and aryl boronic acids.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 95/00363

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A01N 63/00, A01N 41/06, G02C 13/00, A61L 2/18
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A01N, G02C, A61L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAPLUS, WPI, JFIPAT, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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X	CA 2044072 A1 (WEBB, GARTH T.), 8 December 1992 (08.12.92) --	29,41-44
X	EP 0196151 A2 (SAUFLON PHARMACEUTICALS LIMITED), 1 October 1986 (01.10.86) --	29,41-44
X	WO 9317720 A1 (WEBB, GARTH, T.), 16 Sept 1993 (16.09.93) --	29,41-44

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
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"E" erlier document but published on or after the international filing date
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"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 95/00363

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International application No.
PCT/DK 95/00363

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